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RESEARCH ARTICLE

Design, development and *in-vitro* evaluation of diclofenac taste-masked orodispersible tablet formulations

Marie Guhmann[1,2], Maren Preis[3], Frédéric Gerber[2]*, Norbert Pöllinger[2], Jörg Breitkreutz[3], and Werner Weitschies[1]

[1]*Department of Pharmacy, Institute of Biopharmaceutics and Pharmaceutical Technology, University of Greifswald, Greifswald, Germany,* [2]*Glatt Pharmaceutical Services, Technology Center, Binzen, Germany, and* [3]*Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine University of Düsseldorf, Düsseldorf, Germany*

Abstract

Context: Fast onset of action is prerequisite for acute pain medication. A palatable orodispersible medicine of diclofenac providing rapid analgesic effect should improve patient compliance and treatment.

Objective: In the present study, diclofenac taste-masked orodispersible tablets (ODTs) with fast release characteristics were developed. Different taste-masking approaches and formulation concepts were screened *in vitro* for candidate selection.

Materials and methods: Diclofenac was used as free acid. Five taste-masked microgranule formulations were prepared by wet granulation and/or coating processes, and compressed to ODTs. Citric acid (pH-modifying agent) and Eudragit® E PO (amino methacrylate copolymer) were used as taste-masking agents. Evaluation criteria were (i) disintegration time, (ii) processability and (iii) *in-vitro* dissolution profiles in simulated saliva (pH 7.4, 5 mL, 3 min) and compendial pH-change media (paddle, 50 rpm). The prototypes were compared to reference ODTs (without taste-masking). Most suitable ODT prototypes were selected and further evaluated for taste-masking efficiency using an electronic tongue.

Results and discussion: In simulated saliva, the drug was slower released from the prototypes (between 1.1% and 15.5%) than from reference ODTs (23.7%). Less dissolved particles are thus expected *in vivo* for taste perception. Two ODT prototypes showed fast and complete drug release in phosphate buffer. The formulation providing the most efficient taste-masking was selected guided by electronic tongue data.

Conclusion: A novel palatable and fast acting diclofenac ODT formulation was successfully developed. Formulation design, development and *in-vitro* evaluation used in this study may serve as rational approach for manufacturing taste-masked orodispersible dosage forms.

Keywords

Diclofenac, electronic tongue, ODT, taste, taste-masking

History

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Introduction

Oral drug delivery is the preferred and most popular route of administration owing to its versatility, ease of administration and the highest degree of patient compliance[1]. In this area, recent trends in pharmaceutical research focus on the development of innovative drug delivery systems addressing in particular the needs for more patient-friendly and compliant medicines[2]. Thus, the progress in pharmaceutical formulation design has prompted the development of oral solid dosage forms with improved degree of palatability, patient acceptability and enhanced performance. Among new technologies advanced for facilitating medication, orodispersible systems like orodispersible tablets (ODTs) are increasingly successful. ODTs are unit dosage forms having the ability to rapidly disintegrate in the mouth as soon as they come in contact with saliva, allowing the ease of swallowing provided by a liquid formulation[3]. Due to these properties, ODTs offer advantages like administration without the need of water, ease of swallowing and convenience of dosing. Therefore, they have gained considerable attention as a preferred alternative to conventional products, e.g. traditional tablets and capsules[4]. During the last decade, the demand for ODTs has been ever-increasing and the field has become a rapidly growing drug delivery platform in pharmaceutical industry[5].

The specific design of ODTs involves additional issues in comparison to conventional products, especially related to the short residence in the oral cavity. During this time frame, the drug dissolution may start, and so, potentially expose dissolved molecules to the taste buds of the human tongue[6,7]. Formulating unpleasant tasting active pharmaceutical ingredients (APIs) is therefore highly critical when developing an ODT formulation and drug taste-masking techniques are often involved[7].

Optimizing a product for the patient by masking the bad taste of the drug should not compromise the intended bioperformance,

*Present address: Frédéric Gerber, Novartis Pharma AG, Novartis, 4002 Basel, Switzerland

Address for correspondence: Prof. Dr. Werner Weitschies, Institute of Pharmacy, Center of Drug Absorption and Transport, University of Greifswald, Felix-Hausdorff-Strasse 3, 17487 Greifswald, Germany. Tel: +49 3834 864 811. Fax: +49 3834 864 886. E-mail: werner.weitschies@uni-greifswald.de

i.e. the intended *in-vivo* drug release should be ensured to achieve an optimal patient treatment. This is even more challenging when formulating a taste-masked orodispersible dosage form requiring a rapid therapeutic effect. Although no or only negligible dissolved drug amounts should be available in the oral cavity to guarantee the taste-masking efficiency, an early drug release in the gastrointestinal (GI) tract is a prerequisite for its rapid dissolution and absorption. Moreover, the selection of appropriate formulation prototypes should be based on specific characterization methods reflecting the key attributes of the product. Besides the drug release from the formulations and the peculiar manufacturing aspects of ODTs (e.g. short disintegration time, small dimensions, processability), the taste-masking efficiency should be considered in depth.

Taste assessment in pharmaceutical development is not easy. In an early stage, *in-vitro* analytical methods (e.g. drug dissolution testing) are often used as an alternative to human test panels and animal models[8,9]. These methods have increasingly evaluated the release of the drug in a dissolution medium intended to simulate saliva. However, the dissolution tests were often not performed under realistic conditions (e.g. medium pH and composition, residence time) experienced by an oral formulation in the mouth[10,11]. Therefore, it is quite unlikely that the *in-vitro* drug release profiles obtained under these conditions are predictive for *in-vivo* performances. ODT formulations have been rarely studied *in vitro* under mouth-predictive conditions[12]. Therefore, a better simulation of the physiological conditions experienced by ODT formulations after administration during oral disintegration could give a deeper insight of their taste features.

In a later stage, in particular, when the taste investigation of multi-component formulations is concerned, taste sensing analytical devices, also known as electronic tongues, have attracted an ever increasing attention[13]. They can be used in the development of taste-masked ODTs as a decisive evaluation tool for the selection of a final formulation[12].

Diclofenac is a well-known potent non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties[14]. To date, no diclofenac ODT formulation has been commercially available. The design of a novel diclofenac orodispersible medicine providing fast acute pain relief could improve patient compliance, acceptability and treatment. However, diclofenac has an unpleasant taste and leads to irritation of oral mucosa[12,15]. Therefore, the palatability of an orodispersible formulation is a major challenge.

In the present work, taste-masked ODTs comprising diclofenac acid providing fast drug release were developed with different taste-masking strategies and further evaluated *in vitro* based on the desired quality target product profile. A pH-modifier and an amino methacrylate pH-sensitive copolymer were used as taste-masking agents by means of wet granulation and fluidized bed coating processes. A comparative study of the prepared ODTs was performed applying dissolution testing under mouth biorelevant conditions as a supplementary tool to compendial testing in order to determine suitable prototypes. Preliminary selected formulations were further discriminated based on taste qualities using an electronic tongue to choose the final formulation.

Materials and methods

Materials

Diclofenac free acid was purchased from Aarti Drugs (Mumbai, India). Diclofenac sodium and diclofenac potassium were obtained from Unique Chemicals (Mumbai, India). Amino methacrylate copolymer, Eudragit® E PO, was generously provided by Evonik (Nordrhein-Westfalen, Germany). Sodium laurylsulfate was purchased by Fluka (St. Gallen, Switzerland). Sodium stearyl fumarate, Pruv®, and hydrogenated vegetable oil, Lubritab®, were supplied by JRS Pharma (Rosenberg, Germany). Croscarmellose sodium, Ac-Di-Sol® and microcrystalline cellulose, Avicel® PH 101, were received from FMC BioPolymer (Philadelphia, PA). Stearic acid, stearic acid 50 powder, was obtained from Mallinckrodt (St. Louis, MO), magnesium stearate from Merck (Darmstadt, Germany), talc from Selectchemie (Zurich, Switzerland), mannitol, Pearlitol® 160C, from Roquette (Lestrem, France), sucralose, Splenda® sucralose from Tate & Lyle (London, UK), colloidal silicon dioxide, Syloid® 244 FP, from Grace Davison (Gebeng, Germany) and povidone, Kollidon® CL from BASF (Ludwigshafen, Germany).

Quinine hydrochloride was purchased from Caesar & Loretz (Hilden, Germany). Potassium chloride was acquired from Grüssing (Rimsting, Germany). Tartaric acid was purchased from Sigma-Aldrich (Munich, Germany). Water was demineralized by reverse osmosis. Distilled water was obtained by in-laboratory distillation of demineralized water. Absolute ethanol (purity 99.8%) was purchased from VWR International. Hydrochloric acid (1 M) and potassium hydroxide solution (0.1 M) were acquired from Merck. The saturated AgCl inner solution for sensors and reference electrodes, consisting of 3.33 M potassium chloride in saturated silver chloride solution, was provided by Insent (Atsugi-chi, Japan). All chemicals used were of analytical grade.

Preparation of taste-masked microgranules

Taste-masked diclofenac free acid microgranules were manufactured by wet granulation and/or coating, and further incorporated into ODTs. Citric acid, a pH-modifying agent, and an amino methacrylate copolymer, Eudragit® E PO (pH-sensitive and permeable/soluble in gastric fluid of pH value $\leq$5.0), were used as taste-masking agents. As the tablets are intended to disintegrate into the mouth, any perception of the microgranules on the tongue, i.e. any ''gritty sensation'', should be avoided. Therefore, at the end of the granulation and/or coating processes the microgranules were in the 50–350 µm range with d_{50} of about 150 µm. The detailed compositions of the different microgranules and corresponding ODT formulations are given in Table 1 and compared to ''reference ODTs'' for which no taste-masking approach was used.

Preparation of Eudragit® E PO aqueous dispersion

The Eudragit® EPO dispersion was prepared by first dispersing sodium laurylsulfate in half of the final water amount during 5 min using dissolving disk. Then, stearic acid was added and the suspension was steered with an Ultra-Turrax device (IKA, Germany). After 5 min, Eudragit® EPO was incorporated and the suspension was steered with dissolving disk over night (minimum 6 h). Subsequent to this time, magnesium stearate and talc were separately dispersed in the rest of water amount during 5 min using an Ultra-Turrax device. Then, the two suspensions were mixed together and steered with dissolving disk during 30 min. Finally the dispersion was sieved through a 0.2 mm sieve. When used for further processing, stirring of the dispersion was maintained during the whole process.

Wet granulation method

The taste-masked microgranules of formulations F1–F3 were manufactured by, first, pre-mixing diclofenac free acid particles together with appropriate excipients in a Glatt Vertical Granulator VG 10 (Glatt, Binzen, Germany) for 2 min. Then, the mixture was moistened with either water (formulation F1) or Eudragit® E PO

aqueous dispersion (formulations F2 and F3) by means of a 1.2 mm diameter binary nozzle and processed into microgranules until adequate size was reached. The granulation process was followed by a drying step at 40 °C temperature in a Glatt fluidized bed unit GPCG 1.1 (Glatt) until the loss-on-drying (LOD) value of the dried pellets was <1%.

Coating method

Coating of diclofenac crystals

The taste-masked microgranules of formulation F4 were produced by granulation/coating applying 20% w/w of Eudragit® E PO aqueous dispersion directly onto diclofenac free acid particles using a fluidized bed Glatt unit GPCG 1.1 (Glatt) in top-spray configuration. The fluidized bed coater was filled with drug particles and the dispersion was sprayed with a 1.0 mm diameter binary spray nozzle at 0.5 bar atomizing air pressure, 30 m^3/h inlet air volume and 25 °C product temperature. The spray rate was about 25 g/min. Finally, the microgranules were dried at 40 °C product temperature until the LOD value of the dried microgranules was <1%.

Coating of diclofenac microgranules

The taste-masked microgranules of formulations F5 were manufactured with a two-step process. Initially, microgranules were built by premixing diclofenac free acid particles together with appropriate excipients in a Glatt Vertical Granulator VG 10 (Glatt) for 2 min. Then, the mixture was pre-moistened with water by means of a 1.2 mm diameter binary nozzle until a LOD value of about 15% was reached. The pre-moistened mass was subsequently spheronized with water in a Glatt rotor fluidized bed CPS 3 (Glatt) using a 45° rotor plate angle and four flat blades until adequate size was reached. The spray rate was about 25 g/min and the rotor speed was 800 rpm during the spraying phase. The drying step was carried out at 40 °C temperature in a Glatt fluidized bed unit GPCG 1.1 (Glatt). The LOD value of the dried microgranules was <1%.

In the second step, the taste-masking was applied on the prepared microgranules applying 20% w/w coating level of Eudragit® E PO aqueous dispersion. The dispersion was sprayed with a 1.0 mm diameter binary spray nozzle at 1.5 bar atomizing air pressure, 50 m^3/h inlet air volume and 25 °C product temperature. The spray rate was about 5–10 g/min. Finally, the microgranules were dried at 40 °C product temperature until the LOD value was <1%.

Determination of the moisture content

The residual moisture content of the prepared microgranules was evaluated off-line by LOD method using a halogen moisture analyzer Mettler-Toledo HB 43 (Mettler-Toledo, Greifensee, Switzerland) at 105 °C and 1 mg/30 s.

Preparation of ODTs

ODTs of 23.25 mg drug load were obtained by compressing the microgranules of formulation trials F1–F5 (Table 1). Accurately weighted microgranules were dry blended and pre-mixed together with the excipients of the outer phase using a Turbula T2C mixer (Willy Bachofen, Muttenz, Switzerland) for 10 min. The pre-mixed mass was compressed using an eccentric tablet press Korsch EK0 (Korsch, Berlin, Germany) equipped with 10 mm flat faced punches with beveled edges. Reference ODTs were obtained by direct compression of a pre-blended mixture of drug particles and excipients. The prepared tablets were of about 250 mg weight, 2.8 mm height and 20–30 N hardness.

Physical characterization of ODTs

The ODTs of each batch were characterized for weight with a Mettler Toledo PB 303 electronic balance (Mettler-Toledo, Paris, France), thickness using a thickness tester Compac SVH.2,

Table 1. Composition of the taste-masked formulations F1–F5 compared to reference ODTs.

	Amount (% w/w)					
Component	Reference	F1	F2	F3	F4	F5
Granules						
Diclofenac acid	–	10.00	9.81	46.95	83.33	41.67
Mannitol	–	81.50	81.93	–	–	–
Crospovidone	–	3.00	2.94	9.38	–	–
Microcrystalline cellulose	–	2.00	1.96	37.56	–	41.67
Citric acid	–	2.00	–	–	–	–
Sucralose	–	0.50	0.49	–	–	–
Hydrogenated vegetable oil	–	1.00	0.98	–	–	–
Eudragit® E PO	–	–	1.08	3.48	9.52	9.52
Sodium laurylsulfate	–	–	0.11	0.35	0.95	0.95
Stearic acid	–	–	0.16	0.53	1.44	1.44
Magnesium stearate	–	–	0.11	0.35	0.95	0.95
Talc	–	–	0.43	1.40	3.81	3.81
Total	0.00	100.00	100.00	100.00	100.00	100.00
ODTs						
Diclofenac acid	9.30	–	–	–	–	–
TM granules	–	97.00	97.00	19.81	11.16	22.32
Mannitol	81.20	–	–	70.69	80.34	69.18
Crospovidone	3.00	–	–	3.00	3.00	3.00
Microcrystalline cellulose	2.00	–	–	2.00	2.00	2.00
Talc	1.00	1.00	1.00	1.50	1.00	1.00
Sucralose	0.50	–	–	0.50	0.50	0.50
Hydrogenated vegetable oil	1.00	–	–	–	1.00	–
Silicon dioxide	1.00	1.00	1.00	1.50	1.00	1.00
Stearic acid	1.00	–	–	–	1.00	–
Sodium stearyl fumarate	–	1.00	1.00	1.00	–	1.00
Total	100.00	100.00	100.00	100.00	100.00	100.00

Type 523 G (Compac, Meyrin, Switzerland) and hardness by means of a hardness tester Schleuniger 6D (Schleuniger, Allschwil, Switzerland). The disintegration time was evaluated according to the *Eur. Pharm.* using a Sotax disintegration tester DT3 (Sotax, Thun, Switzerland)[16].

Dissolution testing

The release of diclofenac from intermediate formulations (taste-masked microgranules) and final formulations (ODTs) was evaluated using a biorelevant and a compendial (paddle) dissolution test method.

Biorelevant method

With the aim of evaluating *in vitro* the amount of diclofenac that can be released in the oral cavity, the drug release was assessed under mouth-biorelevant conditions. The biorelevant dissolution medium and the experimental design were as proposed previously[12]. The drug exposure to the oral cavity was simulated by 3 min in 5 mL of simulated salivary fluid (SSF) adapted from the literature[14]. The pH value of the medium set at 7.4 was adjusted referring to the human physiological pH range[17]. The very small physiological volume of saliva (5 mL) can hardly be used for dissolution studies. Therefore, the test sample and the test volume of SSF were increased both to the same extent; in detail the equivalent of 10 sample units or 5 units of Voltaren® Dispers (232.5 mg of diclofenac content) were tested in 50 mL of SSF. Samples were taken after 0.5, 1, 1.5, 2, 2.5 and 3 min, respectively. As *in vivo* some particles might remain in the mouth after swallowing the disintegrated ODT, an additional sample was taken at 5 min[12]. The temperature of the dissolution medium was maintained at $37 \pm 0.5\,^{\circ}$C. The paddle speed was set at 50 rpm. All experiments were performed in triplicate.

Subsequent to the *in-vitro* dissolution testing, the pH of the dissolution medium was determined at the end of the study, in order to evaluate whether the formulation composition of each intermediate and final products has an influence on the micro-environment tested. As diclofenac solubility is strongly pH-dependent, a correlation may be established between the pH of the dissolution medium and its ability to dissolve in there. Measurements were performed using a pH meter Seven Easy equipped with an InLab Exper Pro pH-electrode (Mettler-Toledo, Greifensee, Switzerland).

Three milliliters of samples were withdrawn manually (with sample replacement by fresh media) using 5 mL Fortuna Optima syringes (Sigma-Aldrich, St. Louis, MO) fitted with stainless tubings connected to 10 μm poroplast filters (Erweka, Heusenstamm, Germany). The samples were filtered through 0.22 μm PVDF membrane filters (Whatman, Kent, UK) discarding the first 1 mL. Drug adsorption onto the filters was checked by HPLC and confirmed to be negligible. Drug release was analyzed by HPLC. For dissolution tests in SSF, the samples collected from the experiments were immediately injected into the HPLC system after filtration. The HPLC analysis was performed using a Perkin Elmer (Perkin-Elmer, Waltham, MA) equipped with a binary pump 200, a diode array detector 235C, an autosampler ISS 200 and a thermostated column. Diclofenac samples were analyzed using a Xterra MS C8 5 μm column (length 150 mm, internal diameter 3.9 mm) (Waters, Milford, MA) and a C8 pre-column Security Guard Cartridge System kit (Phenomenex, Zwingen, Switzerland). The mobile phase comprised a mixture of methanol and phosphate buffer solution pH 2.5 ± 0.05 70:30 with 1 mL/min flow rate (isocratic mode). The column temperature was 25 °C and the detection wavelength was set at 254 nm. The injection volume was 3 μL for assay determination. The retention time for diclofenac time was about 6 min.

Compendial method

A compendial dissolution method was performed to assess *in vitro* the drug release in the GI tract. The pH-change method (official method for delayed-release articles, USP method ''A'') was applied with a Sotax dissolution apparatus type II (paddle) model AT7 (Sotax). For 2 h, drug release was tested in 750 mL of 0.1 N HCl pH 1.1 before said media was replaced by phosphate buffer (1000 mL). The temperature of the dissolution media was set at $37 \pm 0.5\,^{\circ}$C. The paddle speed was kept at 50 rpm. The samples taken reflected 23.25 mg drug load. The sampling points were at 30, 60, 90 and 120 min in the acidic stage and at 5, 10, 15, 20, 30, 40, 50 and 60 min in the buffer stage. Five milliliters of samples were withdrawn automatically by the sampling device and fed back into the dissolution vessel after analysis. After filtration through a glass microfiber filter Whatman GF/D (Whatman, Dassel, Germany), the cumulative drug release was monitored online using a UV spectrophotometer Perkin-Elmer Lambda 25 (Perkin-Elmer) operating at 276 nm.

In-vitro taste assessment

All measurements were performed *in vitro* using the taste sensing system TS-5000Z (Insent Inc.). The electronic tongue was equipped with seven lipid membrane sensors labeled according to the different taste qualities bitterness (three sensors), sourness, saltiness, umami and astringency and corresponding reference electrodes. The underlying measurement principle is potentiometric and consequently sensor responses were obtained as mV values. According to the Nernst or Nikolsky-Eisenmann equation (Equation 1), the output of the potentiometric chemical sensors is logarithmically dependent on the substance activity[18,19].

$$U = U^0 + (RT/zF)\ln a_i \tag{1}$$

where U is the electrode potential, U^0 corresponds to the standard electrode potential, R is the universal gas constant, T denotes the temperature (K), z is the ionic valence of the substance, F is the Faraday constant and a_i is the substance activity.

$$a_i = f_i c_i \tag{2}$$

where c_i is the substance concentration and f_i denotes the activity coefficient of the substance.

Three sensors are specific for bitterness: bitterness sensor 1 (SB2AC0) and 2 (SB2AN0) detect cationic substances, whereas bitterness sensor 3 (SB2C00) detects anionic substances. The other sensors represent the gustatory stimuli umami (SB2AAE), saltiness (SB2CT0), sourness (SB2CA0) and astringency (SB2AE1). Furthermore, a corresponding ''aftertaste'' can be measured from molecules still adhering to the sensor surface after a short cleaning procedure. The Insent system has been qualified regarding specificity, linearity, range, accuracy, precision, detection and quantification limit as well as robustness, based on the International Conference on Harmonization (ICH) guideline Q2[20].

A 0.5 mM quinine hydrochloride solution was prepared as external standard with demineralized water as this concentration is in the linear range of all sensors[20]. Two washing solutions, for negatively and positively charged sensors, respectively, were made by diluting absolute ethanol to ethanol 30% with distilled water and adding 100 mM hydrochloric acid for the negatively charged sensors or 100 mM potassium chloride and 10 mM potassium hydroxide for the positively charged sensors. A standard solution serving as cleaning and also as reference solution was prepared by dissolving 30 mM potassium chloride and 0.3 mM tartaric acid in distilled water.

A drug load of 23.25 mg was set for each sample, or unit, tested, i.e. taste-masked microgranules or ODTs per prototype.

The experimental design was as proposed previously[12,21]. For taste evaluation, 20 units were dispersed in 100 mL of purified water and stirred for about 3 min; with Voltaren® Dispers 46.5 mg, 10 units were used accordingly. This concentration adequately simulates the intake of one dose which disintegrates in a volume of 5 mL[21]. Particles were subsequently removed by microfiltration using a syringe fitted with a 0.22 µm Whatman glass microfiber filter (Whatman) and the resulting clear solution was analyzed. All preparations were compared to corresponding drug-free formulations.

Before starting the experiments, each sensor (TecLabS Europe, Essen, Germany) was filled with 0.2 mL of saturated AgCl inner solution (inner solution). The reference electrode was completely filled up with inner solution. All sensors were preconditioned in standard solution for one day before the start of the measurements. A sensor check was conducted routinely before every measurement to ensure that the sensors were stable in the correct mV range. Each test sample was measured four times with the remaining sensors. One measurement cycle consisted of measuring a reference solution (Vr), followed by the sample solution (Vs), a short (2×3 s) cleaning procedure, and measurement of the aftertaste (Vr') in reference solution. The aftertaste was measured by determining the change of membrane potential caused by adsorption of the substance to the lipid membrane after the short cleaning procedure. Sensor output for taste (relative value (R)) and sensor output for aftertaste (change of membrane potential caused by adsorption (CPA) value) were calculated in relation to the preliminary determined sensor response to the reference solution (Vr).

$$R = Vs - Vr \tag{3}$$

$$CPA = Vr' - Vr \tag{4}$$

The whole measurement procedure was performed for all samples and repeated afterwards up to four times. For further data treatment the first run was discarded, as recommended by the supplier, in order to enable adequate conditioning of the sensors.

Data collected by the electronic tongue were reviewed and the last three replicates out of four assays were treated by statistical methods. Results were expressed as raw data in mV of the sample relative measurement to the reference. Sensor signal results were evaluated as such or after multivariate data analysis. Multivariate analysis, i.e. principal component analysis (PCA), was used to reduce the multidimensional space (seven independent sensors) into a two-dimension plot. Using PCA, the most abundant information contained in original data could be transformed into the first principal component (PC-1). The second most abundant information is transformed into the second component (PC-2). By this means, information from the raw data can be extracted in order of importance. For the placebo sample and the sample with test compound, a cluster can be obtained in a PCA map by plotting PC-1 against PC-2. This map shows the discrimination and similarities between different samples and groups. For multivariate data analysis, raw data were pretreated by mean centering and scaling to unit variance. Data processing, graphical illustration and statistical interpretation of the results were carried out using Excel 2007 (Microsoft, Redmond, WA) and SIMCA-P + v12.0.1 (Umetrics, Umeå, Sweden).

Results

Physical characterization of ODTs

In Table 2, ODT formulations F1–F5 are compared to reference ODTs with regards to their physical characteristics. A good reproducibility of weight (about 250 mg), height (about 2.7 mm) and hardness (20–30 N) was observed for each prototype (SD values $\leq 5\%$). All formulations disintegrated within less than 3 min in agreement with the specification of the *European Pharmacopeia*. Formulation F1 disintegrates after 2 min 43 s. Formulations F3–F5 show similar disintegration behaviors to the reference formulation. Based on compression force results, formulations F2–F5 could be better compressed than the reference and F1 formulations.

Dissolution testing

Biorelevant method

In Figure 1, the different formulations prepared (taste-masked microgranules and corresponding ODTs) are compared to reference ODTs in terms of the dissolution profiles of diclofenac in simulated saliva. The pH value of each dissolution medium contained in the vessels at the end of the experiment is reported in Table 3. The drug release profile observed from all formulations is slower than that from reference ODTs when tested in SSF for up to 3 min. The cumulative drug releases range from 1.3% (F1 ODTs) to 17.5% (F2 ODTs) after 3 min compared to 26.5% for reference ODTs. The lowest drug releases in SSF are observed with formulations F1 and F5 with 1.3% and 2.4% diclofenac released, respectively, within 5 min in SSF. The taste-masked microgranules show similar drug release to their corresponding ODTs. Based on this observation, it seems likely that the microgranules are not damaged during the compression process.

At the end of the dissolution tests, the dissolution medium pH values were comprised between 7.31 (reference ODTs) and 5.37 (ODTs F1). In case of reference ODTs, the pH value remained almost unchanged until the end of the study (the pH value was lowered by only 1.2%). In contrast, the pH value of the dissolution medium was decreased for all formulations. The decrease in pH value was only slight in case of the formulations F2–F5 (from 6.2% (ODTs F5) to 9.1% (ODTs F3)), whereas it was considerably higher for formulations the F1 (22.3% for microgranules, 27.4% for ODTs).

By correlating these results obtained during the dissolution testing, it seems obvious that the more the pH is reduced during the experiment, the slower are diclofenac release profiles.

Table 2. Comparative characteristics of the prepared diclofenac ODTs compared to reference ODTs. Weight, thickness and hardness are expressed in mean ± SD ($n = 10$); disintegration time in mean ($n = 6$).

Formulation	Weight (mg)	Height (mm)	Hardness (N)	Compression force (kN)	Disintegration time (min:s)
Reference	252 ± 1.4	2.65 ± 0.01	24.9 ± 1.91	10.0	00:17
F1	245 ± 2.1	2.58 ± 0.03	28.4 ± 1.55	9.5	02:43
F2	253 ± 2.1	2.75 ± 0.01	22.5 ± 1.65	6.0	00:09
F3	250 ± 1.1	2.75 ± 0.03	21.6 ± 1.26	7.5	00:30
F4	252 ± 1.3	2.65 ± 0.02	23.6 ± 1.35	7.0	00:16
F5	248 ± 1.4	2.69 ± 0.02	21.2 ± 1.75	7.8	00:15

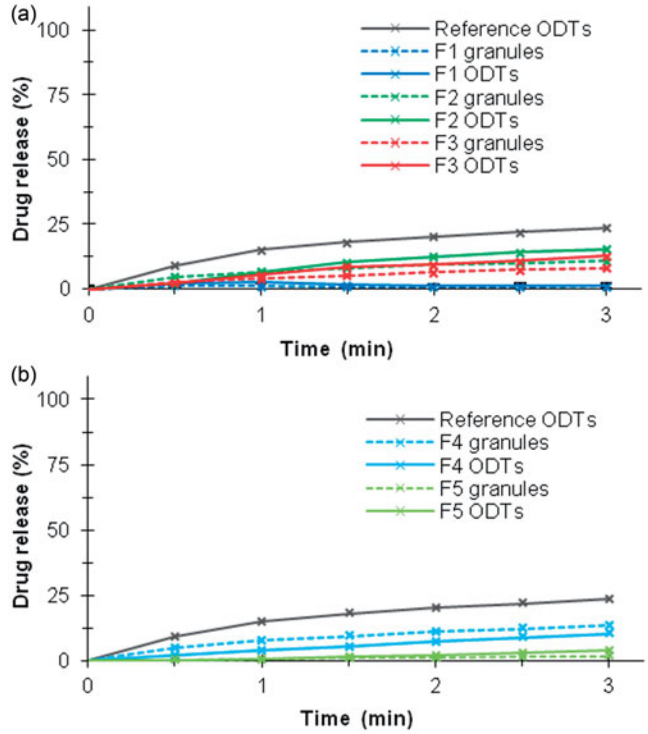

Figure 1. Comparative dissolution profiles of diclofenac TM formulations versus reference ODTs in simulated salivary fluid (SSF) using biorelevant method. The formulations F1–F3 are shown in (a) and the formulations F4 and F5 in (b).

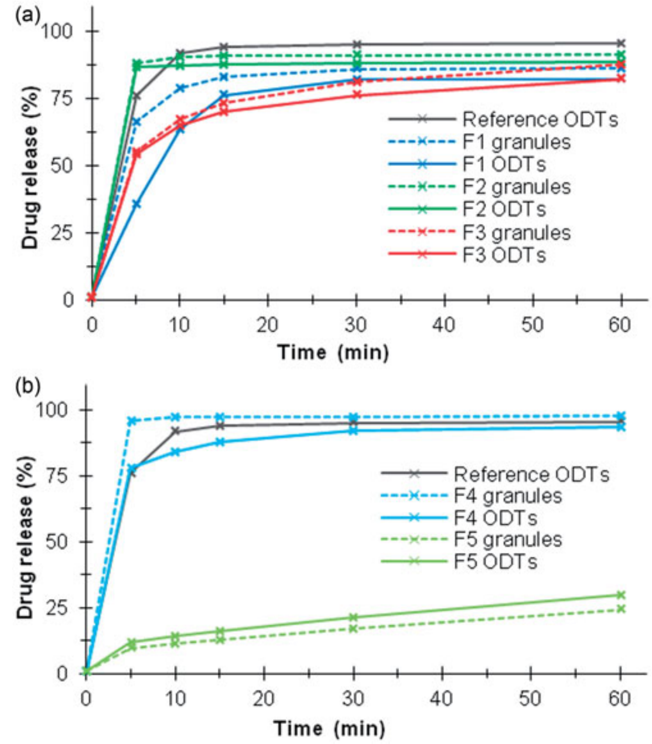

Figure 2. Comparative dissolution profiles of diclofenac TM diclofenac formulations phosphate buffer pH 6.8 after 2 h pre-acidic stage using compendial dissolution method. The formulations F1–F3 are shown in (a) and the formulations F4 and F5 in (b) versus reference ODTs.

Table 3. Comparative pH value measured at the end of the dissolution study in simulated saliva.

Formulation	Formulation step	pH value	Reduction in pH value (%)
Reference	ODTs	7.31	1.2
F1	Granules	5.75	22.3
	ODTs	5.37	27.4
F2	Granules	6.87	7.2
	ODTs	6.78	8.4
F3	Granules	6.96	5.9
	ODTs	6.73	9.1
F4	Granules	6.87	7.2
	ODTs	6.83	7.7
F5	Granules	7.15	3.4
	ODTs	6.94	6.2

Compendial method

Figure 2 shows the dissolution profiles of the taste-masked formulations prepared after pH change from an acidic stage (2 h) to phosphate buffer pH 6.8 using the compendial dissolution test method.

After 2 h of contact with the acidic medium (0.1 N HCl), about 4% of diclofenac was released and dissolved from all tested formulations. In phosphate buffer, very distinct dissolution profiles were observed. Reference ODTs showed fast and complete drug release after 10 min. From formulations F1–F4, diclofenac was completely released within 60 min in buffer of pH 6.8 (Figure 3a and b). A faster drug release ($\geq$80% after 30 min) was achieved with formulations F2 and F4. ODTs prepared with these formulations provided a complete drug release after 5 min and 15 min. Drug release from formulation F5 was considerably delayed (Figure 3b). About 25% of diclofenac was released from both taste-masked microgranules and tablets within 60 min.

In most cases, similar drug release pattern was observed for the intermediate and the final products. For formulations F1, the drug release from the ODTs was slower than from the taste-masked microgranules (about 35% compared to about 66% release of diclofenac after 5 min).

In-vitro taste assessment

The initial screening of the different ODT prototypes was based on specific *in-vitro* evaluation criteria. These criteria were focused on (i) appropriate physical characteristics of the tablets (as e.g. rapid disintegration, compressibility), (ii) low drug release in simulated saliva and (iii) fast and complete drug release in simulated intestinal conditions (the site of absorption of diclofenac). Based on these characteristics and on the results obtained in this study, the most suitable ODT formulations in terms of efficient taste-masking and rapid drug release were determined. Formulations F2 and F4 were selected as adequate candidates. For a more detailed *in-vitro* evaluation and discrimination of these two prototypes, their taste attributes were assessed by means of electronic tongue measurements. Particular attention was given to represent both the intermediate products (taste-masked microgranules) and the final products (ODTs).

Figure 3 shows the PCA map plotting electronic tongue data obtained with the sensors representing bitterness, sourness and astringency. The plot was used in order to discriminate the prototype formulations from their corresponding placebos. The main variance is covered by the first component (PC-1), the *x*-axis. The smaller part of the variance covered by the second principal component (PC-2) is shown on the *y*-axis. About 65% of the total information is represented by PC-1 and 30% by PC-2. The differentiation between the samples should therefore be established mainly regarding PC-1, with additional information

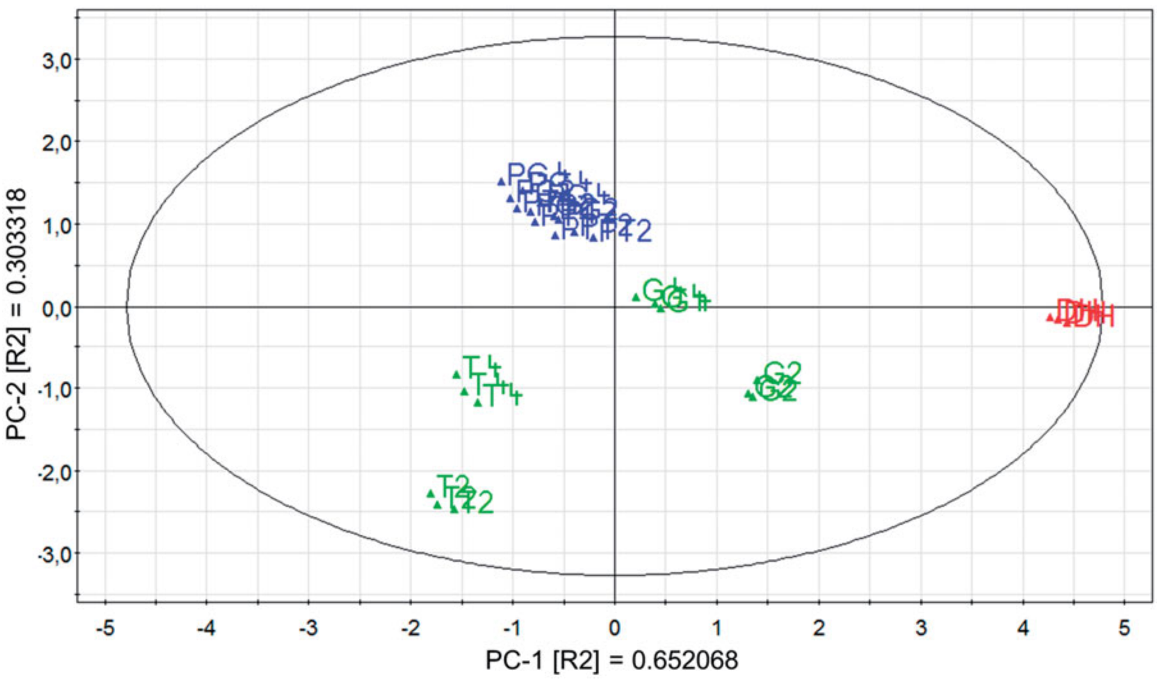

Figure 3. Multivariate data evaluation of diclofenac acid pure API (DH), formulations F4 (TM microgranules G4 and ODTs T4) and formulations F2 (TM microgranules G2 and ODTs T2) compared to their respective placebos (PG4, PT4, PG2 and PT2). The principal component analysis (PCA) map is built with output values of the sensors corresponding to bitterness, sourness and astringency; mean ± SD ($n = 3$).

provided by PC-2. The effect of the taste-masking approach and the formulation concept on the taste qualities of the tested samples can be evaluated with the electronic tongue outputs. The configuration of the PCA map provides the system discrimination power between the samples.

As shown in Figure 3, all formulations were detected as being different from the pure drug (DH) and also from each other. Small clusters were observed for each sample indicating that reproducible analysis was achieved. All placebo formulations are located in the same cluster. Sensor responses to the pure API are at the extreme right-hand part of the *x*-axis. Responses induced by the prototypes are distributed on the lower side of the map. Considering PC-1, responses from the taste-masked microgranules are located between those from the pure drug and placebos; responses from the ODTs overcome the responses of their corresponding placebos. The plot output data show that formulation F4 taste-masked microgranules and ODTs (represented as G4 and T4, respectively, in Figure 3) are located closer to their corresponding placebos than those of formulation F2 (G2 and T2). In more details, according to the electronic tongue, the formulations F4 are more similar to placebo although the formulations F2 show longest distance to the pure drug. As the electronic tongue is used as a comparative tool, formulation F4 was chosen as the investigation aim was to find the most pleasant-tasting formulation. Indeed, it can be assumed that a drug-free formulation has a pleasant taste compared to the bitter tasting pure diclofenac. Better taste qualities and more efficient drug taste-masking of formulation F4 ODTs could thus be suggested.

With the aim of deeper evaluating the taste modalities provided by the most palatable ODT formulation, ODTs F4 were deeper investigated with the electronic tongue and compared first to their corresponding placebo and second to a commercially available formulation of diclofenac free acid in the form of dispersible tablets (i.e. Voltaren® Dispers).

The outputs for taste and aftertaste induced by each sample on the sensors are expressed in Table 4. Comparing the data from ODTs F4 to the data from their placebos and the pure drug, it is possible to estimate the reduction for each taste and aftertaste sensations achieved. As can be seen from the data, a reduction in the drug detection is observed for all sensors for taste (38.2–94.8%) as well as aftertaste (10.6–51.8%) sensations.

Comparing the taste and aftertaste sensor data from the tablets F4 and Voltaren® Dispers, it can be seen that both the prepared formulation and the commercial product induce markedly different sensor responses to those of pure diclofenac; except for the saltiness sensor for which the responses are similar. This effect is consistent to the diclofenac form used in this study, i.e. the free acid and not one of the salts (e.g. sodium or potassium); the saltiness sensor might not be responding. For the discriminative sensors, similar electrical outputs were observed.

Discussion

Orodispersible drug delivery systems like ODTs consist of unit solid dosage forms comprising medicinal substances that disperse typically within few seconds in the mouth before swallowing[5]. The *European Pharmacopoeia* requirement (disintegration time $\leq$3 min) is easily achieved as the ODTs tested disintegrate within few seconds to about 1 min[22]. Therefore, ODTs efficiently respond to the need for more patient compliant and effective dosage form[14]. Not available so far, the development of a diclofenac ODT formulation with fast release characteristics should improve patient acceptance and treatment.

Diclofenac is mainly used in three forms: the free acid as well as its sodium and potassium salt. Although most of the commercial diclofenac oral solid dosage forms comprise its salts (i.e. Voltaren® in the form of delayed release (DR) and sustained release (SR) tablets with the sodium salt or in the form of immediate release (IR) tablets with the potassium salt), interest has also raised for the free acid form of the drug.

For the development of an ODT formulation providing in particular a fast onset of analgesic action, the use of diclofenac free acid offers advantages compared to the salt forms. Indeed, better organoleptic characteristics are expected for the free acid

Table 4. Comparative taste and aftertaste sensor responses (mV) from the electronic tongue between diclofenac free acid pure API (DH), the selected final ODT formulation F4 (T4), its placebo formulation (PT4) and the commercial product in dispersible tablet form, Voltaren® Dispers (VD); mean ± SD ($n = 3$). The taste reduction (%) achieved for the formulation F4 is also given.

	SB2AC0		SB2AN0		SB2C00		SB2AAE		SB2CT0		SB2CA0		SB2AE1	
	Bitterness 1		Bitterness 2		Bitterness 3		Umami		Saltiness		Sourness		Astringency	
	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)	mV (±SD)	Taste reduction (%)
Taste														
DH	−68.13 (±0.87)		−57.17 (±1.98)		−26.87 (±1.87)		−44.37 (±2.57)		24.86 (±3.83)		−56.48 (±2.60)		97.06 (±4.52)	
T4	−102.65 (±1.67)	91.8	−141.20 (±6.25)	92.2	−166.85 (±3.92)	60.2	−63.93 (±0.84)	88.6	25.82 (±0.30)	38.2	−103.00 (±1.60)	90.3	−85.29 (±4.62)	94.8
PT4	−105.73 (±2.60)		−148.28 (±4.54)		−259.38 (±3.74)		−66.44 (±2.85)		27.37 (±0.85)		−107.99 (±3.12)		−95.35 (±2.56)	
VD	−95.79 (±0.93)		−152.64 (±0.52)		−177.61 (±0.82)		−65.90 (±0.40)		25.16 (±0.46)		−112.11 (±0.92)		−94.08 (±3.05)	
Aftertaste														
DH	0.10 (±0.56)		2.14 (±1.00)		−3.14 (±2.18)		−1.50 (±0.59)		−0.60 (±0.10)		−1.13 (±0.58)		0.24 (±0.05)	
T4	1.59 (±0.65)	40.2	9.54 (±2.07)	51.8	−13.87 (±1.46)	10.6	−1.71 (±0.61)	29.2	−0.78 (±0.09)	45.0	−0.88 (±0.64)	17.4	0.29 (±0.31)	41.7
PT4	3.81 (±0.91)		16.73 (±1.07)		−104.02 (±1.64)		−2.22 (±0.61)		−1.00 (±0.10)		0.31 (±0.66)		0.36 (±0.37)	
VD	1.61 (±0.14)		5.94 (±0.72)		−13.45 (±0.38)		−1.88 (±0.41)		−0.90 (±0.05)		−0.81 (±0.53)		−0.53 (±0.33)	

due to lower solubility properties[12,15]. Furthermore, diclofenac is a lipophilic (log *P* 4.4; log *D* 1.4 at pH 6.8) and poorly soluble weak acid (pKa 4.0) characterized by a pH-dependent solubility[14]. Accordingly, the drug is highly sensitive to physiological pH modifications encountered along the mouth and the GI tract. In the mouth, the weakly acidic to neutral pH environment (6.2–7.4 pH range) likely promotes dissolution of drug particles that can be detected by the tongue taste buds and overcome the drug taste threshold[17]. To avoid any unpleasant taste stimulation, a taste-masking process should prevent drug release from ODTs in saliva during the product residence in the oral cavity.

Because of low solubility properties at acidic pH, the dissolution of diclofenac is considered to be very poor in the stomach. Precipitation events may rather be expected *in vivo*. However, a fast release in the gastric fluid is a prerequisite for providing rapid onset of action. By this means, drug particles in the stomach can be directly available for dissolution in the upper small intestine, the site of absorption of diclofenac.

Recently, it has been shown *in vitro* that the residence of diclofenac salts in acidic media simulating the gastric fluid is likely to cause critical behaviors of the drug. Indeed, a marked precipitation behavior of diclofenac salts, i.e. sodium and potassium salt, was demonstrated in the literature; this precipitation was further associated with an irregular agglomeration of drug particles[23]. Such behaviors were also particularly observed when the swallowing procedure was simulated, i.e. when the drug salt forms contacted simulated saliva in connection with simulated GI fluids. This *in-vitro* phenomenon was suggested to be responsible for the multiple absorption peaks observed after dosing diclofenac salts from solutions, suspensions, effervescent or dispersible formulations[23]. Almost no precipitation and no formation of agglomerates were observed with diclofenac free acid. The free acid proved to better withstand extremes changes in conditions along the mouth and the GI tract *in vitro*[23]. For these reasons, the free acid was chosen in this study as the most suitable drug form to prepare a taste-masked diclofenac ODT formulation.

So far, taste-masking technologies are mostly based on the reduction of the drug solubility in saliva in order to maintain drug concentration below the taste threshold[24]. Among others, common approaches include addition of flavoring and/or sweetening agents, adjustment of pH values, ion exchange resin adsorption, prodrug approach, microencapsulation, solid dispersion method, freeze-drying, implement complexation and supercritical fluids[24]. More lately, the innovation in taste reduction techniques has presented taste suppressant compounds acting directly on different types of taste receptors, as e.g. by blocking gap junctions of channels and hemichannels[25,26]. However, recent trends are getting towards more cost effective and easy to scale-up techniques[27] among which, much older pharmaceutical processes, like wet granulation and fluidized bed coating, have regained great interest[28].

Commonly used for the development of various pharmaceutical dosage forms, granules or microgranules have been exploited as a mean for the taste-masking of bad tasting APIs[29]. Taste-masked microgranules have already been introduced in the development of different types of oral solid formulations and have been in the late past also described in the production of chewable and rapidly disintegrating tablets[28,30–32]. Applying particular excipients and technologies, lower effective surface area of the drug exposed to the human tongue after oral intake can be achieved. Nevertheless, the reduction of the effective surface area should be efficient enough to mask the drug unpleasant taste[29].

In order to mask the taste of diclofenac free acid, a pH-modifying agent (citric acid) and an amino methacrylate copolymer soluble in gastric fluid of pH ≤5.0 (Eudragit® E PO) were chosen.

Considering the pH-dependent solubility of diclofenac, the use of a pH-modifying agent that has the ability to decrease the microenvironmental pH of the saliva is expected to prevent the drug from dissolving in the mouth. Having a pleasant taste, the well soluble citric acid is the most preferred among the various pH-modifiers available. In addition, the slight acidic and lemon-like taste of this excipient is also quite used to enhance the taste properties of oral formulations and thus, may represent a valuable tool to improve the patient acceptability and compliance[33].

Therefore, this excipient was chosen in this work to develop one formulation (formulation F1) of taste-masked microgranules and compressed into ODTs.

The pH-sensitive polymer Eudragit® E PO was used as a preferred polymeric agent to prepare the other ODT prototypes using different manufacturing technologies and different formulation concepts. Designed to resist in neutral to basic environments like saliva, Eudragit® E PO prevents direct drug exposure to the mouth and thus suppresses or reduces its dissolution in there. After the ODT disintegration, and depending on the formulation concept, embedded-drug particles or drug-loaded multiparticulates are released into the mouth. After swallowing and arrival in the acidic environment of the stomach, Eudragit® E PO dissolves. Then, the drug is easily released from the microgranules and dispersed in gastric fluid, although only slight dissolution can be achieved due to diclofenac poor solubility under such acidic conditions. Finally, subsequent to the gastric emptying, diclofenac is made available to the intestinal fluid for dissolution and absorption. In that case, and eventhough drug dissolution is low in the stomach, fast and complete drug dissolution is intended to be achieved in the basic environment of the intestine. As it is the site of absorption of diclofenac, rapid action, i.e. rapid analgesic effect, can be expected.

ODTs must disintegrate rapidly. Therefore, a prime evaluation criteria for ODTs is the time until complete disintegration is achieved. Several *in vivo* disintegration test methods have been described in the literature[34–36]. Disintegration times measured with said *in-vivo* methods typically vary in the range of few seconds only. *In-vivo* test with human test panels often provide poorly reproducible and reliable results[37]. Moreover, *in vivo* studies in human volunteers may address ethical or safety concerns[37]. Various *in-vitro* disintegration test methods have been described in the literature so far as alternatives to *in-vivo* studies[37]. The texture analyzer is claimed to be the most predictive one[28]. However, in previous work, the compendial, the texture analyzer and the oral disintegration methodologies provided comparable ODT disintegration time results[28].

The compendial disintegration test has therefore been applied further in this study in order to evaluate the disintegration of the tablets prepared. All formulations disintegrate rapidly within less than 3 min, as recommended by the *European Pharmacopoeia*[22]. However, the tablets F1 disintegrated within 2 min and 43 s only. Much shorter disintegration times were observed with the formulations comprising Eudragit® E PO. It was also observed that similar compression force to reference tablets (10 N) had to be applied for the preparation of ODTs F1 (9.5 N). This observation could be explained by the presence of citric acid in the matrix of ODTs F1. Indeed, citric acid is a moisture sensitive compound tending to melt at a temperature above 100 °C; this property allows in particular using citric acid as a binder in hot melt granulation process[38]. The high compression force needed might provide a dense ODT matrix with a longer ability to disintegrate.

Drug dissolution test in simulated saliva was first used to evaluate the taste suppression or reduction in the mouth.

As expected, it was shown that when the formulations F1, i.e. containing citric acid as taste-masking agent, were in contact with simulated saliva for 3 min, the pH value of the dissolution medium was significantly reduced. The more acidic pH in the dissolution medium proved to almost completely suppress the dissolution of diclofenac free acid. Interestingly, slightly less diclofenac was dissolved when formulations F1 were kept more than 1 min in simulated saliva (Figure 1), most likely due to the buffering effect of citric acid. As the ODT tablet progressively disintegrates, the acidic excipient decreases the microenvironmental pH of the simulated saliva reducing the drug solubility. It was shown that the pH of the dissolution medium where the formulations F1 were tested is lowered to values closed to diclofenac pK_a (pH of 5.75 for the taste-masked microgranules, pH of 5.37 for the ODTs). As a result, the solubilization capacity of the drug is likely affected after release leading to its further precipitation. Extrapolating these *in-vitro* results to what would happen *in vivo* in the mouth, or more specifically in the saliva, the lower ability of the drug to dissolve upon administration would be correlated to less or negligible perception of its taste. An ODT formulation as used for the formulation F1 should thus achieve a suitable taste-masking effect. Moreover, the presence of citric acid should provide for a pleasant lemon-like taste.

The formulations prepared with Eudragit® E PO showed lower drug release in simulated saliva than the reference ODTs. However, the taste-masking efficiency of the polymer depends on the formulation concept. Taste-masked microgranules prepared by wet granulation showed similar drug release from a fast disintegrating mixture (formulation F2) or a matrix mixture (formulation F3). The slightly faster drug dissolution observed with ODTs F2 can be explained by the faster disintegration ability of the tablets F2 when fast-disintegrated microgranules are compressed into ODTs and located in the outer phase.

In contrast, when prepared by fluidized bed process, the coated microgranules (formulation F5) are markedly more effectively taste-masked than coated drug crystals (formulation F4). In fact, the previous granulation/spheronization of diclofenac provides perfectly round-shaped microgranules (formulation F5) which are a very adequate starting material for coating application. Finally, these microgranules F5 were surrounded by a dense taste-masking coating layer. When pure drug particles were directly granulated in the fluidized bed, the blackberry-like structure of the taste-masked microgranules produced (formulation F4) did most probably not provide an ideal substrate for taste-masked coating application. Indeed, drug particles might have remained uncovered on the surface after the coating process step and were then able to dissolve.

Comparing both manufacturing processes, the formulations F2 and F4 (taste-masked microgranules and tablets) showed very similar drug release profiles in simulated saliva (about 11% and 13%, respectively, after 3 min).

The taste-masking is a prerequisite when formulating ODT products[39]. However, it must not delay the drug release and compromise the desired fast onset of therapeutic action. In this work, the influence of the taste-masking step was evaluated with a dissolution testing in compendial media pH 1.1 and pH 6.8 simulating the conditions in the intestine after a short residence time in the stomach. Not discriminating in this study, the acidic phase was however a prerequisite to the dissolution of the Eudragit® E PO polymer used in some of the ODT prototypes. In that acidic phase, diclofenac is likely easily released. However, as expected based on diclofenac very poor solubility properties at acidic pH, the drug can only be very slightly dissolved at the end of the acidic phase (about 4%) for all prototypes.

To refer to as dosage forms providing immediate-release characteristics, drug release in the first 30–60 min must be at least 80% in a dissolution medium consistent with its site of absorption *in vivo*[40]. For diclofenac, drug release was evaluated in a dissolution medium of pH 6.8; in which the conditions in the intestine can be simulated. More recently, as an extension of this definition, it is generally assumed that dosage forms releasing at least 80% of the drug in the first 30 min qualify as fast-release profiles.

According to this statement, the ODTs F1, providing the lower dissolution rate under mouth-relevant conditions, and also the ODTs F3 and F5 do not comply with the specification for fast-release characteristics. With different qualities of diclofenac used

in this study, different ODT formulation concepts were achieved. On one hand, microgranules manufactured by wet granulation (i.e. matrix microgranules) provided matrix-type ODTs; on the other hand, coated micropellets ended up as ODTs containing discrete multiparticulates.

Only the matrix-type ODTs F2 prepared by compression of fast-disintegrating microgranules achieved fast-release characteristics; drug release is almost complete after 5 min at pH 6.8. Comprising citric acid, drug release from the ODTs F1 is much slower than from the microgranules. This observation is consistent with a dense/compact ODT matrix obtained after compression that retards the drug dissolution rate. The microgranules F3 (with non fast-disintegrating properties) were blended and compressed with a fast-disintegrating outer phase. The formulation concept in F3 can explain the rapid disintegration of the ODTs but the slower release of diclofenac from the microgranules than from F2.

Diclofenac release and dissolution rate is markedly different from ODTs F4 and F5 containing discrete multiparticulates. As explained previously, the microgranules F4 are coated drug crystals with a blackberry-like structure the surface of which might present uncovered drug particles. Obviously, such uncovered particles have an enhanced ability to dissolve. Moreover, after dissolution, these particles may easily provide available pores to the dissolution medium leading to an even faster microgranules disintegration and drug release/dissolution. ODTs F5 disintegrate in few seconds releasing the microgranules at pH 1.1 where Eudragit® E PO polymer dissolves. Thus, the dissolution profile of ODTs F5 at pH 6.8 (Figure 2) shows the ability of diclofenac to be released from the microgranules and to dissolve. The microgranules F5 matrix only composed of diclofenac and microcrystalline cellulose (ratio 1:1) is highly dense/compact and can likely explain the low ability to disintegrate and release diclofenac.

Based on these results as summarized in Figure 4, formulations F2 and F4 are considered to be the most suitable ODT prototypes. The taste qualities of these prototypes were investigated in details using the Insent TS-5000Z electronic taste sensing system. Previous work had demonstrated the ability of this electronic tongue to discriminate different ODT multi-component formulations and also to highlight the taste-masking effect[12]. A multivariate evaluation of the sensor responses suggests that with

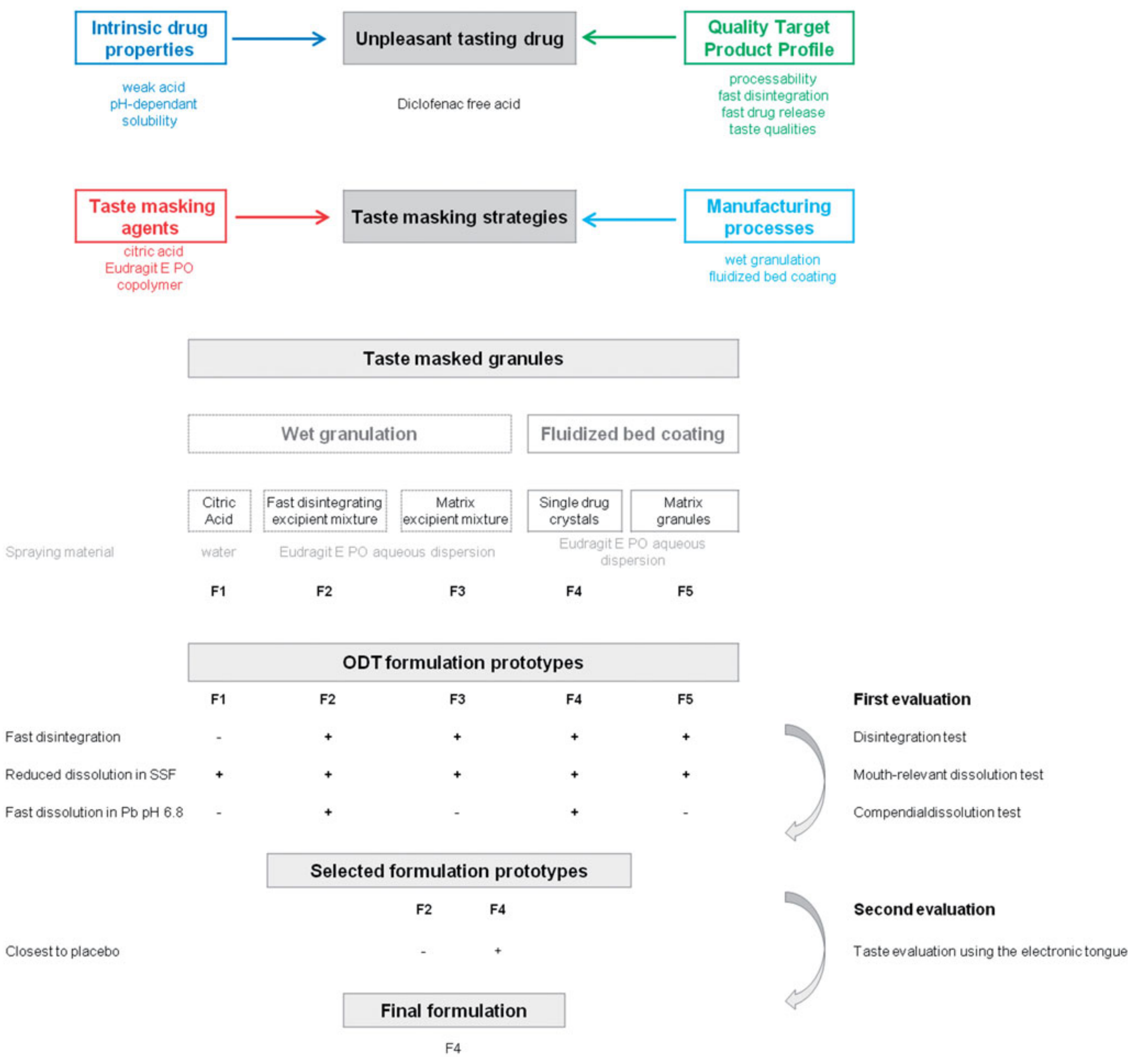

Figure 4. Rational approach used for the formulation design, development and evaluation diclofenac TM ODTs.

formulations F2 and F4 (taste-masked microgranules and ODTs) a successful taste-masking effect can be achieved (Figure 3). All formulations, prepared with the same taste-masking agent, could be discriminated by the electronic tongue although similar drug release profiles were observed with the *in-vitro* method under mouth-relevant conditions. Better taste-masking is observed for formulations F4 than for F2 with clusters located closer to their placebos.

The Quality Target Product Profile is a precious guiding tool in pharmaceutical formulation development that allows considering both drug product quality and patient benefit[41]. For ODTs, this concept involves an appropriate choice of taste-masking approaches and formulation designs to development/screen drug products in a preliminary stage; and select rationally the most suitable prototype(s) according to the desired product attributes in a second stage.

Based on the specific properties of diclofenac, the challenge to design a novel taste-masked ODT formulation with fast-release characteristics focuses on the following *in-vitro* and *in-vivo* features: (i) fast disintegration with minimum drug release in simulated saliva (taste suppression or reduction in the mouth), (ii) drug release in acidic conditions (dispersed drug particles in the stomach) followed by (iii) fast and complete dissolution in neutral to basic conditions (fast dissolution and absorption in the upper small intestine, enhanced bioavailability, fast onset of action). Besides the peculiar physical aspects of ODTs (e.g. rapid disintegration, small dimensions, processability), these key features represent decisive evaluation criteria for the candidate selection.

In this study, the most efficient taste-masking approach of diclofenac was achieved when diclofenac drug crystals were microgranulated and finally coated with an Eudragit® E PO dispersion. Said taste-masked microgranules were successfully processed to physically stable ODTs providing the intended fast drug release.

The performance of orodispersible dosage forms like ODTs likely approaches that of solutions when the drug completely dissolves in the mouth; or suspensions when the dissolution is incomplete. In a consistent manner, it is also true for dispersible formulations where the dosage form is already disintegrated at the time of administration. The new ODT formulation selected in the work additionally showed very similar drug release and taste qualities than the commercially available dispersible tablet formulation Voltaren® Dispers (Figure 5), when tested under identical *in-vitro* conditions. Therefore, the results obtained in this study may be promising for the development of a new diclofenac ODT formulation and may provide a pharmaceutical and commercial interest.

Conclusion

In the present study, a novel fast-acting and palatable diclofenac ODT formulation was designed. Different taste-masking approaches and ODT formulation concepts were screened by means of key product attributes including processability, rapid disintegration, fast drug release and taste qualities. For diclofenac free acid, the amino methacrylate copolymer Eudragit® E PO was found to be an efficient taste-masking agent. Investigating the different prototypes, multiparticulate ODTs demonstrated enhanced *in-vitro* properties compared to matrix ODTs. In addition, the granulation/coating of pure drug crystals applying a fluidized bed process proved to be an efficient process to achieve the key product attributes being improved taste qualities and fast drug release. In combination with compendial methods, the use of dissolution testing under mouth-relevant conditions was applied in order to select taste-masked prototypes in a first stage.

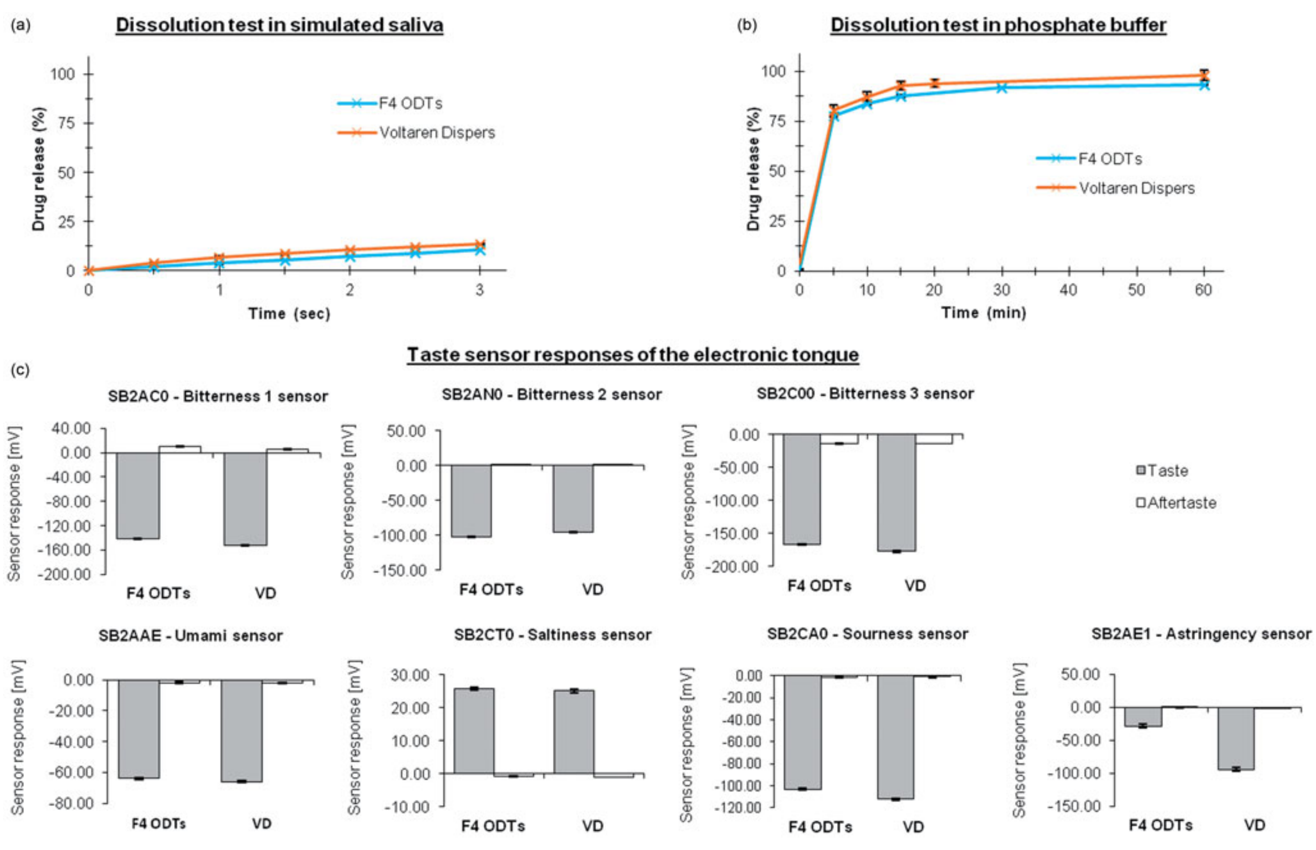

Figure 5. Comparative evaluation of the novel ODT formulation of diclofenac (F4 ODTs) and the marketed dispersible tablets Voltaren® Dispers (VD): drug release in simulated saliva using biorelevant method (a), drug release in phosphate buffer after 2 h pre-acidic stage using compendial dissolution method (b) and taste sensor responses of the electronic tongue (c); mean ± SD ($n = 3$).

Besides, the electronic tongue was used as a tool for the final candidate selection in a second stage. This study may serve for the rational development of taste-masked orodispersible dosage forms.

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Declaration of interest

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